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Blood glucose, acid–base and electrolyte changes during loading doses of alpha2-adrenergic agonists followed by constant rate infusions in horses

Ringer, Simone K ; Schwarzwald, Colin C ; Portier, K ; Mauch, J ; Ritter, A ; Bettschart-Wolfensberger, Regula

Abstract: The aim of the present study was to investigate changes in blood glucose concentration ([Glu]B), acid-base status and electrolyte concentrations during constant rate infusions (CRI) of two alpha2-adrenergic agonists in seven horses treated in a blinded, randomised, crossover design with xylazine or romifidine. An intravenous (IV) bolus of xylazine (1mg/kg) or romifidine (80μg/kg) was administered followed by an IV CRI of xylazine (0.69mg/kg/h) or romifidine (30μg/kg/h) for 2h. Blood samples were collected from the pulmonary artery before and after loading doses, during the CRI, and for 1h after discontinuing drugs. Blood glucose, base excess (BE), pH, partial pressure of carbon dioxide ($Pv^{-}CO2$), strong ion difference (SIDest) and bicarbonate concentration ([Formula: see text]) increased significantly during the CRI with both alpha2-adrenergic agonists. Chloride concentration ([Cl-]B) and anion-gap (AG) decreased significantly compared to baseline. The decrease in sodium concentration ([Na+]B) was only significant with xylazine. From 1h after starting the CRI onwards, [Glu]B was significantly higher with romifidine compared to xylazine. Except [Glu]B, SIDest, and $Pv^{-}CO2$, all variables returned to normal values 1h after discontinuing xylazine. After stopping romifidine, all variables except pH remained altered for at least 1h. It was concluded that loading doses of alpha2-adrenergic agonists followed by CRIs produce [Glu]B, acid-base and electrolyte changes. The clinical significance of the reported changes remains to be investigated and absolute values should be interpreted with caution, as fluid boli were used for cardiac output measurements, but may become important during prolonged infusion and in critically ill patients.

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Blood glucose, acid–base and electrolyte changes during loading doses of alpha$_2$-adrenergic agonists followed by constant rate infusions in horses

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ABSTRACT

The aim of the present study was to investigate changes in blood glucose concentration ($[Glu]_B$), acid–base status and electrolyte concentrations during constant rate infusions (CRI) of two alpha$_2$-adrenergic agonists in seven horses treated in a blinded, randomised, crossover design with xylazine or romifidine. An intravenous (IV) bolus of xylazine (1 mg/kg) or romifidine (80 μg/kg) was administered followed by an IV CRI of xylazine (0.69 mg/kg/h) or romifidine (30 μg/kg/h) for 2 h. Blood samples were collected from the pulmonary artery before and after loading doses, during the CRI, and for 1 h after discontinuing drugs.

Blood glucose, base excess (BE), pH, partial pressure of carbon dioxide ($P\bar{v}CO_2$), strong ion difference (SID_{est}) and bicarbonate concentration ($[HCO_{3\ std}^-]_B$) increased significantly during the CRI with both alpha$_2$-adrenergic agonists. Chloride concentration ($[Cl^-]_B$) and anion-gap (AG) decreased significantly compared to baseline. The decrease in sodium concentration ($[Na^+]_B$) was only significant with xylazine. From 1 h after starting the CRI onwards, $[Glu]_B$ was significantly higher with romifidine compared to xylazine. Except $[Glu]_B$, SID_{est}, and $P\bar{v}CO_2$, all variables returned to normal values 1 h after discontinuing xylazine. After stopping romifidine, all variables except pH remained altered for at least 1 h.

It was concluded that loading doses of alpha$_2$-adrenergic agonists followed by CRIs produce $[Glu]_B$, acid–base and electrolyte changes. The clinical significance of the reported changes remains to be investigated and absolute values should be interpreted with caution, as fluid boli were used for cardiac output measurements, but may become important during prolonged infusion and in critically ill patients.

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Introduction

Alpha$_2$-adrenergic agonists are routinely used for sedation and analgesia in veterinary medicine (Dart, 1999) and administration as an intravenous (IV) constant rate infusion (CRI) is becoming more frequent (Lamont et al., 2012; Ringer, 2012). The main advantages of alpha$_2$-adrenergic agonists in humans are the potent sedative and analgesic effects with minimal respiratory depression and less postoperative delirium compared to other drugs (Hoy and Keating, 2011). In human intensive care units (ICUs) interest in CRI of alpha$_2$-adrenergic agonists is increasing (Tan and Ho, 2010; Hoy and Keating, 2011). This tendency is also observed in veterinary critical care patients (Posner and Burns, 2009).

Concerns regarding alpha$_2$-adrenergic agonists mainly reflect their cardiovascular (CV) effects (England and Clarke, 1996; Murrell and Hellebrekers, 2005; Tan and Ho, 2010), and many studies have been designed to examine the CV effects of alpha$_2$-adrenergic agonist CRIs in horses (Bettschart-Wolfensberger et al., 1999; Ringer et al., 2013a). However, the use of alpha$_2$-adrenergic agonists is also associated with other side effects that might be less obvious, but may have important consequences, especially in critically ill patients. For example, hyperglycaemia is associated with worse outcomes in proportion to the elevations in blood glucose concentration ($[Glu]_B$) in human medicine (Klonoff, 2011). Hyperglycaemia is also associated with diuresis, which has been described following single doses of alpha$_2$-adrenergic agonists in horses (England and Clarke, 1996) and other species (Ambrisko and Hikasa, 2002; Kanda and Hikasa, 2008; Talukder and Hikasa, 2009; Murahata and Hikasa, 2011).

Despite the increasing use of alpha$_2$-adrenergic agonists, including in critically ill animals (Posner and Burns, 2009), changes in $[Glu]_B$, electrolyte concentrations and acid–base status during CRIs of alpha$_2$-adrenergic agonists remain insufficiently studied. Additionally, the different alpha$_2$-adrenergic agonists used as a CRI have not been compared regarding their effects on $[Glu]_B$,

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electrolytes and acid–base status. Xylazine and romifidine are both registered alpha$_2$-adrenergic agonists commonly used in equine clinical practice. Romifidine is more alpha$_2$ receptor-selective than xylazine or detomidine, but less than medetomidine (Muir, 2009). The aim of the present study was to investigate the effects of xylazine and romifidine CRIs on $[Glu]_B$, acid–base balance and electrolytes in horses, and to compare the two drugs.

Materials and methods

The study was approved by the Ethical Committee of the National Veterinary School of Lyon (0807, 13 May 2008) and was performed using blood samples obtained during a cardiovascular study reported elsewhere (Ringer et al., 2013a).

For the concurrent cardiovascular study, seven research horses (six French Standardbreds and one French Saddlebred; 8.7 ± 1.75 years; 515.2 ± 52.96 kg) were catheterised with Swan-Ganz thermodilution catheters placed in the pulmonary arteries. The catheters were advanced through 8.5F introducer sheaths (Intro-flex, Edwards Lifesciences) that had been previously placed in the jugular vein.

After catheterisation, two baseline blood samples (B1, B2) were collected 10 min apart from the pulmonary artery. Blood samples were collected anaerobically into blood gas syringes (BD A-Line, BD Diagnostics) and immediately analysed using a point-of-care blood gas system including a co-oximeter (Rapidpoint 400, Siemens Medical Solutions Diagnostics).

Blood gases were analysed at 37 °C without correcting for the horses' temperature. The blood gas analyser measured pH, partial pressure of carbon dioxide ($P\bar{v}CO_2$), $[Glu]_B$, and blood electrolyte concentrations (sodium $[Na^+]_B$, chloride $[Cl^-]_B$, and potassium $[K^+]_B$). The anion gap (AG), standard bicarbonate concentration $[HCO^-_{3\ std}]_B$, and base excess of the extracellular compartment (BE_{ecf}) were calculated automatically by the analyser. Strong ion difference was estimated (SID_{est}) by manual calculation using the formula: $SID_{est} = [Na^+]_B - [Cl^-]_B$. Preliminary reference values for the blood gas analyser were determined including 15 healthy horses and were defined as means ± 2 SD.

Horses were treated in a blinded, randomised, crossover design with xylazine or romifidine. A 16-day washout period was allowed between treatments. After baseline measurements, horses were sedated with xylazine (Xylasol, Dr. E. Graeub) (1 mg/kg) or romifidine (Sedivet, Boehringer Ingelheim) (80 μg/kg) given IV over 3 min by manual injection through the side arm of one of the introducer sheaths. The start of the loading dose administration was time point 0. Loading doses were followed by xylazine (0.69 mg/kg/h) or romifidine (30 μg/kg/h) CRI for 2 h (time points 3–123 min). The CRIs were delivered by infusion pumps (Syramed μSP6000, Arcomed). Drugs were diluted in 0.9% saline (Chlorure de Sodium 0.9%; Braun Medical) by an unblinded person, so that equal volumes (50 mL loading dose, 25 mL/h CRI) were administered in both treatments.

Beside the CRIs containing alpha$_2$-adrenergic agonists in 0.9% NaCl, the horses did not receive any oral or IV fluids throughout the duration of the study, with the exception of repeated boluses of ice-cold fluids (5% glucose [Braun Medical] in five horses, 0.9% NaCl in two horses) used for cardiac output measurements by thermodilution conducted within the concurrent CV study. Administered bolus doses resulted in average (mean ± SD) 5% glucose doses per hour of 1.3 ± 0.61 mL/kg/h (xylazine treatment) and 1.3 ± 0.65 mL/kg/h (romifidine treatment). The average 0.9% NaCl dose was 1.2 ± 0.64 mL/kg/h (xylazine) and 1.4 ± 0.48 mL/kg/h (romifidine). Cardiac output measurements were done at each time point, always after blood collection. The horses received the same type of fluid during both treatments.

Blood analyses were repeated immediately after finishing loading dose administration (3 min) and thereafter every 10 min during the first hour of CRI (13, 23, 33, 43, 53, 63 min) and every 15 min during the second hour (78, 93, 108, 123 min). The CRIs were discontinued after 2 h (time point 123 min) and data were collected every 15 min for an additional hour (138, 153, 168, and 183 min).

Statistical methods

As there was no difference in results when the horses receiving glucose for cardiac output measurements were analysed separately from the ones receiving saline, data of all seven horses were pooled for statistical analysis. Statistical analysis was performed using SigmaStat 3.5 (Systat Software). Homogeneity of variances was assessed by graphical display of the data and validity of the normality assumption was confirmed by assessment of normal probability plots of the residuals. Two-way repeated measures ANOVA (two within factors) followed by a Holm–Sidak test for multiple comparisons versus a control (time point B1) was used to compare the two treatments and to study changes over time compared to baseline. The level of significance was set at $P < 0.05$.

Results

A significant increase in $[Glu]_B$ was observed during both alpha$_2$-adrenergic agonist infusions (Treatment, $P = 0.001$; Time, $P < 0.001$; Treatment × Time, $P < 0.001$) (Fig. 1). The increase was more pronounced with romifidine compared to xylazine. An increase in $[Glu]_B$ was also observed in horses receiving 0.9% NaCl instead of 5% glucose for cardiac output measurements (Fig. 1).

Significant changes in pH were seen over time and between treatments (Treatment, $P = 0.007$; Time, $P < 0.001$; Treatment × Time, $P = 0.330$) (Fig. 2). There was a significant increase in pH with both alpha$_2$-adrenergic agonists. Overall and already at baseline, pH was significantly higher with romifidine compared to xylazine. Also, a significant increase in BE_{ecf} (Treatment, $P = 0.156$; Time, $P < 0.001$; Treatment × Time, $P < 0.001$) and $[HCO^-_{3\ std}]_B$ (Treatment, $P = 0.057$; Time, $P < 0.001$; Treatment × Time, $P < 0.001$) was observed during both alpha$_2$-adrenergic agonists (Fig. 2). After discontinuing CRIs, the effects on BE_{ecf} and $[HCO^-_{3\ std}]_B$ were longer lasting with romifidine compared to xylazine. During drug administration, a progressive, significant increase in $P\bar{v}CO_2$ (Treatment, $P = 0.40$; Time, $P < 0.001$; Treatment × Time, $P = 0.008$) was seen with both treatments (Fig. 2). With romifidine the $P\bar{v}CO_2$ remained increased 1 h after discontinuing CRI.

With both alpha$_2$-adrenergic agonists a significant decrease in $[Cl^-]_B$ was observed (Treatment, $P = 0.080$; Time, $P < 0.001$; Treatment × Time, $P < 0.001$) (Fig. 3). Effects on $[Cl^-]_B$ were more prolonged with romifidine. A significant decrease in $[Na^+]_B$ was detected over time for xylazine, but not for romifidine (Treatment, $P = 0.021$; Time, $P = 0.056$; Treatment × Time, $P = 0.031$) (Fig. 3). Already at baseline, $[Na^+]_B$ values were significantly lower with romifidine compared to xylazine, and remained significantly lower at different measurement points. No significant changes over time or between treatments were seen for $[K^+]_B$ (Treatment, $P = 0.080$; Time, $P = 0.951$; Treatment × Time, $P = 0.216$) (Fig. 3).

There were no significant differences in SID_{est} between treatments, but with both alpha$_2$-adrenergic agonists a significant increase over time was observed (Treatment, $P = 0.594$; Time, $P < 0.001$; Treatment × Time, $P = 0.057$) (Fig. 4). With xylazine there was a significant decrease in AG during drug administration, while with romifidine a decrease in AG was only observed 1 h after drug discontinuation (Treatment, $P = 0.845$; Time, $P < 0.001$; Treatment × Time, $P = 0.002$) (Fig. 4). A significantly lower AG was

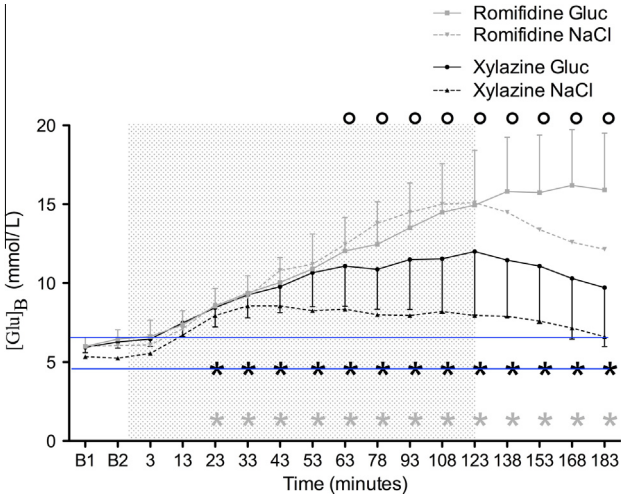

Fig. 1. Blood glucose concentration ($[Glu]_B$: mean ± SD) measured before loading doses of xylazine and romifidine (B1, B2), immediately after loading dose administration (3 min), during 2 h of CRI (3–123 min), and for 1 h after discontinuing CRI (123–183 min). Five horses received 5% glucose (continuous lines) and two received 0.9% NaCl (dashed lines) for cardiac output measurements. Dotted area shows drug administration time. ✱ Significant difference (Holm–Sidak, $P < 0.05$) compared to the baseline (B1) of the same treatment. ○ Significant difference (Holm–Sidak, $P < 0.05$) between treatments Blue lines represent (mean ± 2 SD) values obtained in 15 healthy horses.

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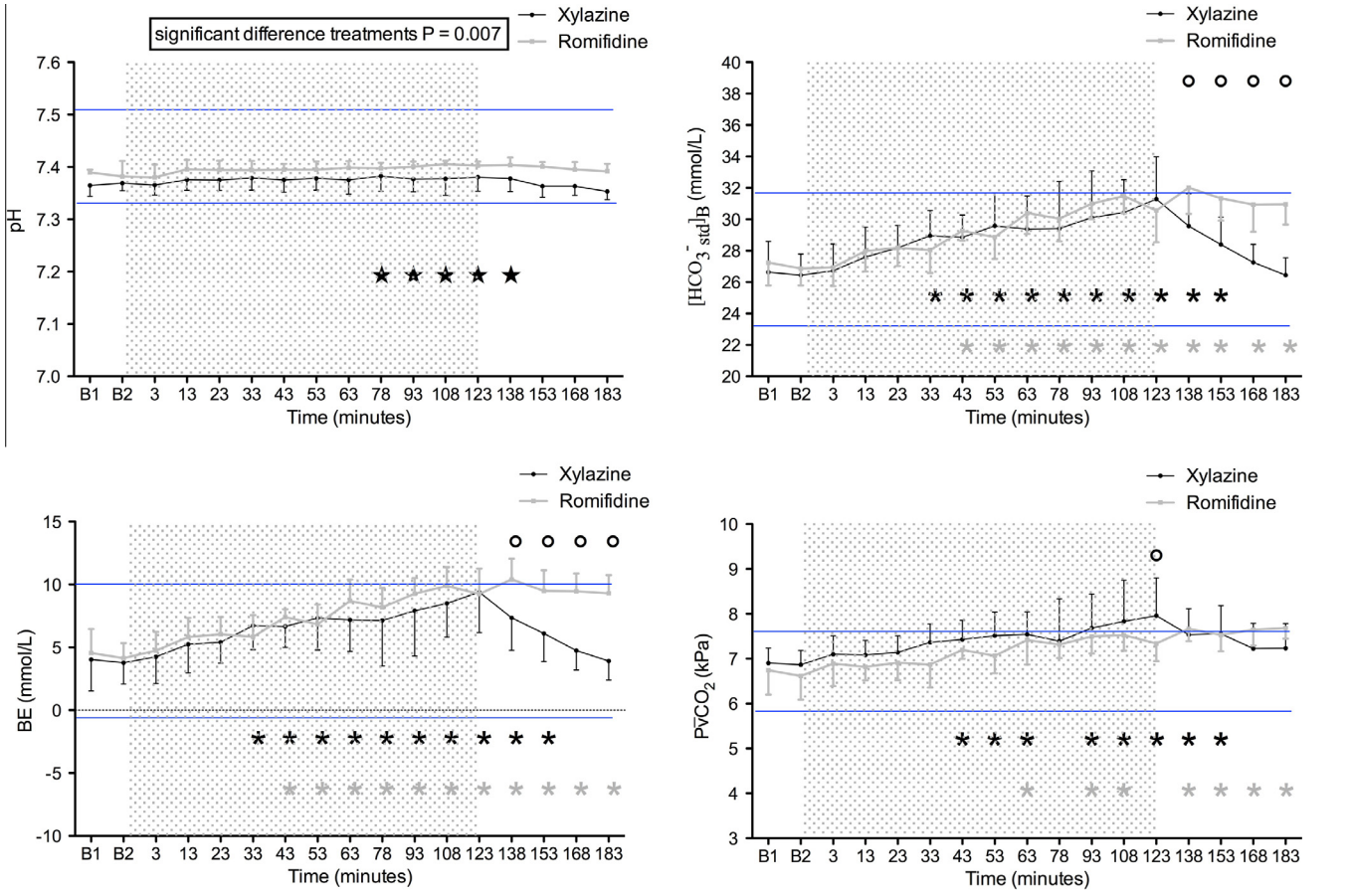

Fig. 2. Measurements of pH, mixed venous partial pressure of carbon dioxide ($PvCO_2$), base excess (BE) and blood bicarbonate ($[HCO_3^-{}_{std}]_B$) concentration (mean ± SD) in seven horses before loading doses of xylazine and romifidine (B1, B2), immediately after loading dose administration (3 min), during 2 h of CRI (3–123 min), and for 1 h after discontinuing CRI (123–183 min). Dotted area shows drug administration time. ✱, ○ Key in Fig. 1. ★ Both treatments significant difference compared to baseline (B1). Blue lines represent (mean ± 2 SD) values obtained in 15 healthy horses.

observed with xylazine compared to romifidine at the end of CRI (123 min). After discontinuing CRI, with xylazine the AG increased rapidly, leading to a higher AG compared to romifidine at 183 min.

Discussion

The results of this study indicate that both xylazine and romifidine significantly alter $[Glu]_B$, electrolyte concentrations and acid base balance when administered as a bolus followed by a CRI during 2 h in healthy horses.

An increase in $[Glu]_B$ has been described in the horse after administration of single doses of different alpha$_2$-adrenergic agonists (England and Clarke, 1996) and during detomidine CRI combined with buprenorphine (van Dijk et al., 2003). However, to our knowledge this is the first time effects on $[Glu]_B$ were studied during CRIs of alpha$_2$-adrenergic agonists as sole agents in horses.

Postsynaptic alpha$_2$-adrenergic receptors of the pancreatic β-cells are involved in insulin regulation (Ruohonen et al., 2012) and probably play an important role in the hyperglycaemic effect of alpha$_2$-adrenergic agonists. However, other authors have suggested that the effects of alpha$_2$-adrenergic agonist on glycaemic response are not only due to actions mediated by alpha$_2$-adrenergic receptors (Ambrisko and Hikasa, 2002; Kanda and Hikasa, 2008). Other sites of action (e.g. hepatic tissue) and involvement of other receptors such as alpha$_1$-adrenergic receptors and imidazoline receptors have been proposed (Ambrisko and Hikasa, 2002; Kanda and Hikasa, 2008).

In the present study, the increase in $[Glu]_B$ was more pronounced with romifidine compared to xylazine. Differences in hyperglycaemic response between different alpha$_2$-adrenergic agonists have already been described in dogs and cats (Ambrisko and Hikasa, 2002; Kanda and Hikasa, 2008). It has been hypothesised that the high alpha$_2$-adrenergic selectivity of medetomidine compared to other alpha$_2$-adrenergic agonists is most likely responsible for its less pronounced (i.e. non-significant) effect on plasma glucose concentration in dogs (Burton et al., 1997). However, this is not in agreement with the results of the present study where romifidine, the more alpha$_2$-selective drug, produced a more pronounced effect on hyperglycaemia compared to xylazine.

In human medicine, hyperglycaemia from any cause is associated with worse outcomes in proportion to the elevations in $[Glu]_B$ (Klonoff, 2011). In the present study, $[Glu]_B$ appeared to increase continuously during CRI and to decrease only once alpha$_2$-adrenergic agonists were discontinued. Therefore, even higher $[Glu]_B$ can be expected during more prolonged infusions. Absolute values of the present study should be interpreted with caution, as some horses received repeated boli of 5% glucose solution for cardiac output measurements. In two horses, normal saline was used instead, to see if changes in $[Glu]_B$ were only due to the glucose solution used for cardiac output measurement. In these two horses not receiving 5% glucose solution, an increase in $[Glu]_B$ was also observed, and the increase was larger with romifidine compared to xylazine (Fig. 1). Also, the fact that $[Glu]_B$ decreased after discontinuing alpha$_2$-adrenergic agonists despite continuing cardiac output measurements indicates that the increase observed during

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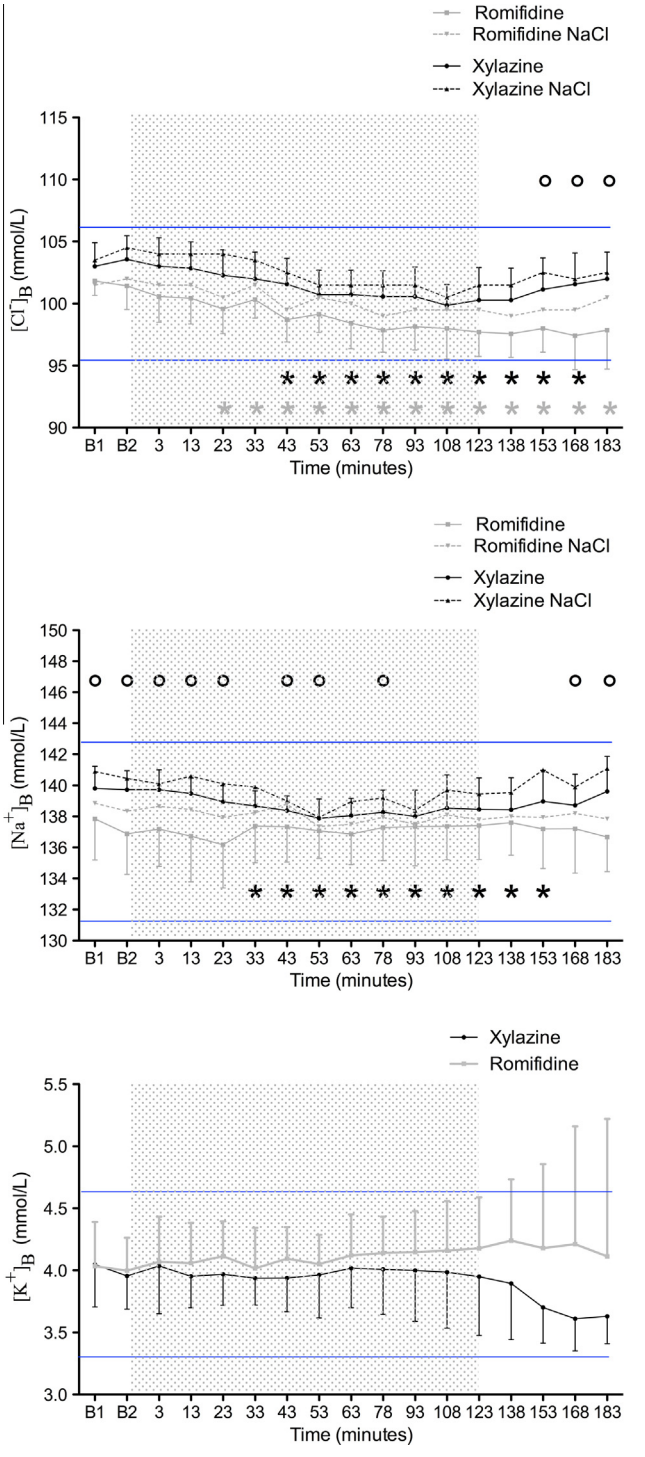

Fig. 3. Measurements of blood sodium $[Na^+]_B$, chloride $[Cl^-]_B$, and $[K^+]_B$ concentrations (mean ± SD) before loading doses of xylazine and romifidine (B1, B2), immediately after loading dose administration (3 min), during 2 h of CRI (3–123 min), and for 1 h after discontinuing CRI (123–183 min). Five horses received 5% glucose solution (continuous lines) and two received 0.9% NaCl (dashed lines) for cardiac output measurements. Dotted area shows drug administration time. ✱, ○ Key in Fig. 1. Blue lines represent (mean ± 2 SD) values obtained in 15 healthy horses.

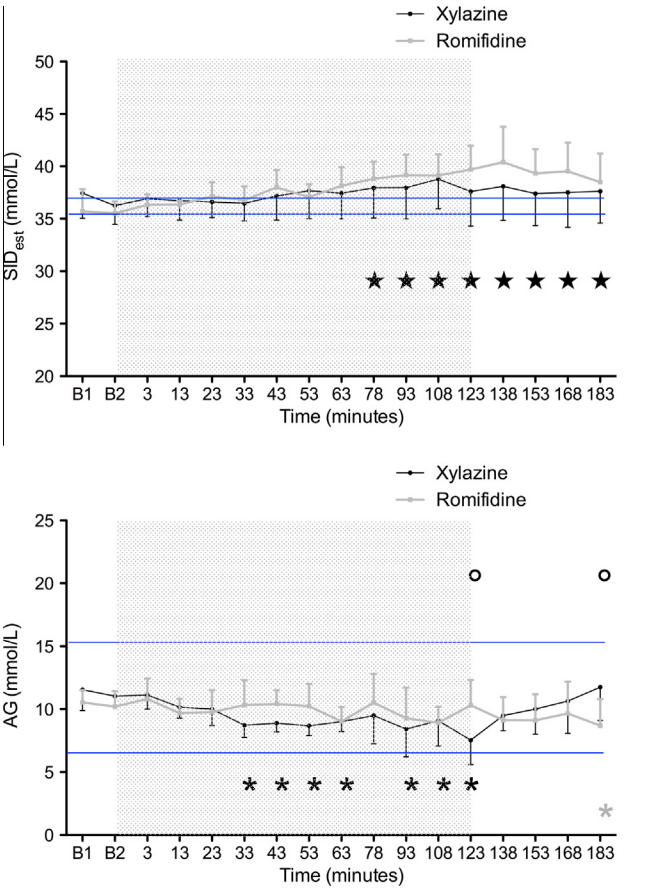

Fig. 4. Estimated strong ion difference (SID_{est}) and anion gap (AG) (mean ± SD) measured in seven horses before loading doses of xylazine and romifidine (B1, B2), immediately after loading dose administration (3 min), during 2 h of CRI (3–123 min), and for 1 h after discontinuing CRI (123–183 min). Dotted area shows drug administration time. ✱, ○ Key in Fig. 1. ★ Both treatments significant difference compared to baseline (B1) Blue lines represent (mean ± 2 SD) values obtained in 15 healthy horses.

alpha$_2$-adrenergic agonist CRI was not only due to 5% glucose administration.

Blood electrolyte concentrations were studied during 3 h of medetomidine–morphine CRI and no significant changes were seen in Na^+, K^+ and Cl^- (Solano et al., 2009). In the present study, a continuous and significant decrease in $[Cl^-]_B$ and increase in SID_{est} was observed during both CRIs. However, the decrease in $[Na^+]_B$ was only significant with xylazine. The SID_{est} can increase due to an increase in plasma Na^+ concentration, a decrease in Cl^- concentration, or a decrease in plasma free water (commonly dehydration) (Autran de Morais and Constable, 2012). Dehydration and hypernatremia are unlikely, since a decrease rather than an increase in $[Na^+]_B$ concentration was observed in the present study. Therefore, the increase in SID_{est} is mostly attributed to the decrease in $[Cl^-]_B$. A decrease in serum $[Cl^-]_B$ has not been reported after alpha$_2$-adrenergic agonist administration before. However, an increased excretion of Cl^- was observed after xylazine bolus administration in horses (Trim and Hanson, 1986).

Effects of alpha$_2$-adrenergic agonists on Cl^- transport have been demonstrated on human cystic fibrosis epithelial and colonic cell lines (Holliday et al., 1997; Norez et al., 2008). However, urinary electrolyte concentrations and fractional excretion of electrolytes in the urine were not investigated in the present study and the exact mechanism leading to the observed electrolyte changes in horses cannot be elucidated. A compensatory hypochloraemic alkalosis in response to the increased $P\bar{v}CO_2$ is unlikely, as there was a simultaneous increase in pH, which would mean that overcompensation had occurred, and this is improbable. Nevertheless, it is interesting that this is the first time that a decrease in $[Cl^-]_B$ has been described related to alpha$_2$-adrenergic agonists.

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Contrary to our results observed with xylazine, no decrease or even a significant increase in serum Na^+ concentration has been observed in other studies using different single doses of alpha$_2$-adrenergic agonists (Thurmon et al., 1984; Trim and Hanson, 1986; Gasthuys et al., 1993; Kullmann et al., 2011; Wojtasiak-Wypart et al., 2012). Nevertheless, an increased Na^+ excretion in urine has been described for horses after romifidine (Gasthuys et al., 1993). No changes in $[K^+]_B$ were observed in the present study. However, effects on serum concentration and urinary excretion of K^+ have been described after single doses of xylazine and romifidine (Trim and Hanson, 1986; Wojtasiak-Wypart et al., 2012).

In our study, a decrease in AG was observed, although with romifidine, the decrease was only significant 1 h after discontinuing CRI. Hypoalbuminaemia is considered the only important cause for a decrease in AG (Autran de Morais and Leisewitz, 2012), although an accumulation of unmeasured cations (e.g., hypercalcaemia, hyperkalaemia and hypermagnesaemia) should be considered as well (Rennke and Denker, 2007). In the present study, there were no significant changes in $[K^+]_B$ and a decrease, rather than an increase in Ca^{2+} has been previously reported after romifidine administration (Wojtasiak-Wypart et al., 2012). However, a decrease in total plasma solids has been described during detomidine CRI (Daunt et al., 1993) and a decrease in total proteins during medetomidine/morphine CRI (Solano et al., 2009). Unfortunately, plasma proteins, albumin, Ca^{2+} and Mg^{2+} were not measured in the present study.

A significant increase in pH, BE_{ecf}, $[HCO_{3\ std}^-]_B$, and $P\bar{v}CO_2$ was observed during both treatments. However pH values remained within physiologically normal limits. An increase in pH has not been reported previously after single doses of the different alpha$_2$-adrenergic agonists (Clarke et al., 1991; Bueno et al., 1999; Yamashita et al., 2000; Freeman et al., 2002; Bettschart-Wolfensberger et al., 2005) or during CRI of medetomidine and detomidine (Daunt et al., 1993; Bettschart-Wolfensberger et al., 1999; van Dijk et al., 2003) in horses. Conversely, a decrease in pH in face of an increase in HCO_3^- was reported during a CRI of medetomidine–morphine (Solano et al., 2009). However, the horses of Solano et al. (2009) underwent laparoscopy with insufflation of carbon dioxide, which was accompanied by a significant increase in $PaCO_2$.

In this study, the increase in pH observed in face of an increase in $P\bar{v}CO_2$, associated with an increase in BE and SID_{est} and a decrease in AG, were indicative of metabolic alkalosis. As already mentioned before, the increase in SID_{est} was probably due to a decrease in $[Cl^-]_B$. Therefore, hypochloraemic metabolic alkalosis was suspected, resulting from an increase in blood $[HCO_{3\ std}^-]_B$ secondary to loss of Cl^- from the body. A significant increase in $[HCO_{3\ std}^-]_B$ was observed for both alpha$_2$-adrenergic agonists. Similar effects on HCO_3^- and BE have been observed after single doses of romifidine (Freeman et al., 2002; Wojtasiak-Wypart et al., 2012) or during medetomidine or detomidine CRI (Daunt et al., 1993; Bettschart-Wolfensberger et al., 1999; Solano et al., 2009) in horses. Unfortunately blood lactate was not measured in the present study. However, based on the rather elevated BE and pH we do not expect an important increase in lactate. This would coincide with previous studies reporting no changes in blood lactate after single doses or CRIs of alpha$_2$-adrenergic agonists in horses (Solano et al., 2009; Kullmann et al., 2011).

The significant differences seen between the two alpha$_2$-adrenergic agonists in the present study might be attributed to the specificity or selectivity for different subtypes of alpha$_2$-adrenergic receptors or collateral effects on other receptors like imidazoline or alpha$_1$-adrenergic receptors, or due to a complex interaction of different mechanisms. The difference might also be dose-dependent. However, the two protocols used in the present study provided the same depth of sedation during CRI, as assessed by the head position in relation to the ground in undisturbed healthy horses (Ringer et al., 2013b). The more prolonged effect of romifidine compared to xylazine after discontinuing drug administration is not surprising, as a prolonged effect of romifidine compared to xylazine has already been shown for sedation and cardiovascular effects (Ringer et al., 2013a,b).

The main limitation of the present study is the use of fluid boli for cardiac output measurements of a concomitant study. This could have had an effect on our absolute values, however not on the comparison between the two treatments, as each individual horse received the same fluid during both treatments. Also the fact that variables tended to normalise after discontinuing alpha$_2$-adrenergic agonists despite continuing cardiac output measurements indicates, that changes were unlikely only due to fluid boli.

The clinical importance of the changes we observed remains to be investigated. However, fact is that with both alpha$_2$-adrenergic agonists mean values of several variables were outside the mean ± 2 SD of the reference values obtained from 15 healthy horses. With both alpha$_2$-adrenergic agonists the changes observed were increasing with duration of CRI. Therefore, aggravation of the effects should be expected during more prolonged infusion. The induced changes should probably also be considered in critically ill patients with pre-existing disturbances in $[Glu]_B$, electrolyte, and acid–base balance, where further alterations in biochemical variables might be crucial. This is critical, as the use of alpha$_2$-adrenergic agonist CRIs to provide sedation, anxiolysis and analgesia is becoming more and more popular in human and small animal ICUs (Posner and Burns, 2009; Tan and Ho, 2010; Hoy and Keating, 2011), and probably in the future also in equine intensive care patients.

However, extrapolation of the present results to different populations should be done with caution, since the effects might depend on the alpha$_2$-adrenergic agonist used, its dose, the duration of administration, the species and the underlying condition and metabolic status of the animal. Therefore, further studies using the different alpha$_2$-adrenergic agonist as a CRI in the different species and under different conditions are recommended to elucidate the relevance of alpha$_2$-adrenergic agonist-induced metabolic changes in clinical patients.

Conclusions

Xylazine and romifidine administered as a CRI had significant effects on $[Glu]_B$, electrolyte concentrations, and acid–base status in horses. Changes become progressively more prominent during CRI, and should be considered in patients receiving prolonged alpha$_2$-adrenergic agonist infusions.

Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

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